Tetrahedron Vol 44, No. 1, pp. 41 to 48, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

SYNTHETIC ROUTES TO CRISTATIC ACID AND DERIVATIVES

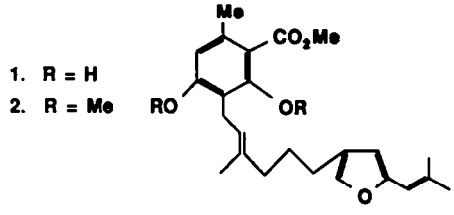
Jack Chiarello and Madeleine M. Joullié*

Department of Chemistry
University of Pennsylvania
Philadelphia, PA 19104 U.S.A.

(*Received in USA* 10 *August* 1987)

Abstract: *Synthetic paths to cristatic acid derivatives are explored and a convergent route to the total synthesis of these molecules is described.*

Cristatic acid (1), a farnesyl phenol modified by incorporation of a furan ring in its side chain, was isolated from the fruiting bodies of *Albatrellus cristatus* by Steglich and co-workers in 1981.[1,2] Biological screening of cristatic acid showed good antibacterial activity against the

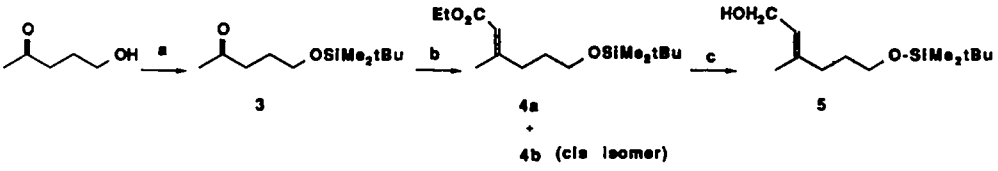


gram-positive bacteria *Bacillus subtilis* and *Bacillus brevis*. The permethylated derivative of 1 (2) did not exhibit antibacterial activity but showed a strong inhibitory effect against cells of the ascites form of Ehrlich carcinoma. The significant changes in biological activity caused by minor changes in functionality suggested that further structural modifications might be appropriate. As a result of these considerations and our previous investigations of fungal metabolites,[3,4] we became very interested in this related series of compounds. An interesting feature common to these molecules is the effect of substituents at the phenolic groups. Alkylation and acylation of these positions have a profound influence on the biological activity. Therefore, further structural modifications of these fungal metabolites could afford potentially valuable therapeutic agents. For this purpose, the design of convergent approaches was essential.

We envisioned a strategy utilizing three main sections of the molecule: (1) the tetrasubstituted aromatic ring; (2) the 2,4-disubstituted furan; and (3) the intervening terpenoid chain. We first examined the terpenoid chain. The key steps in its preparation were: (1) the formation of a *trans* trisubstituted double bond; and (2) the coupling of the chain to the aromatic and heterocyclic moieties. Two routes were explored for the initial coupling. The first would attach the terpenoid side chain to the tetrasubstituted aromatic ring, while the second would attach it to the 2,4-disubstituted furan. In either case, the approach chosen to generate the *trans* trisubstituted olefin was a Horner-Emmons reaction involving triethyl phosphonoacetate. 5-Hydroxy-2-pentanone (Scheme 1) was converted to the corresponding *tert*-butyldimethylsilyl ether (3) in 84% yield. Triethyl phosphonoacetate was then added to sodium hydride, followed by addition of 3. Compounds 4a and 4b were obtained in a 10 to 1 ratio and isolated in 88% yield. Isomer 4a was then reduced with diisobutylaluminum hydride (DIBAL) to afford the corresponding alcohol (5) in 96% yield. Alternatively, treatment of triethyl phosphonoacetate with n-butyllithium at

-78°C, followed by addition of freshly distilled 5-chloro-2-pentanone, gave compounds 6a and 6b in a 1.6 to 1 ratio and 80% overall yield (Scheme 2). Isomer 6a was reduced with diisobutylaluminum hydride and the alcohol (7) was protected as its *tert*-butyldimethylsilyl ether (8) (85% yield). A Finkelstein reaction was used to convert the chloride into the iodide (9), in quantitative yield. All attempts to couple 9 to either 23 or 25 failed.

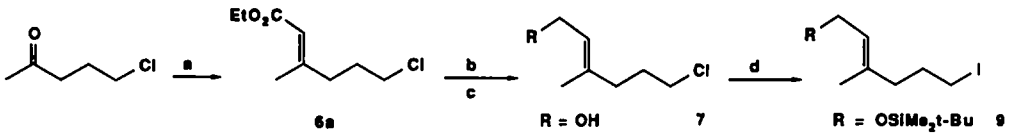
Scheme 1



3 4a + 4b (cis isomer) 5

[a] tert-BuMe$_2$SiCl, imidazole, DMF; [b] NaH, triethyl phosphonoacetate; [c] DIBAL.

Scheme 2



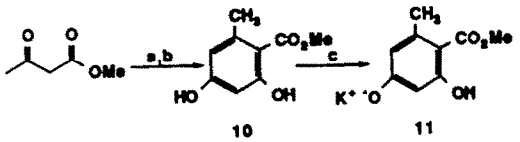
6a + 6b (cis isomer) R = OH 7 R = OSiMe$_2$t-Bu 8 R = OSiMe$_2$t-Bu 9

[a] LDA, triethyl phosphonoacetate; [b] DIBAL; [c] tert-BuMe$_2$SiCl, imidazole; [d] NaI, acetone.

The aromatic moiety, the tetrasubstituted phenol 10, was prepared in one step (60% yield) using a modified version of Barrett's protocol[5] (Scheme 3). Compound 10 was treated with an ethanolic solution of potassium hydroxide to afford 11 in 78% yield. We next examined the coupling of 5 with potassium salt 11 (Scheme 4), hoping to achieve predominantly C-alkylation and regioselective prenylation at the more nucleophilic 3-position. Alcohol 5 was converted to the corresponding allylic bromide (12) under standard conditions. The crude bromide (12) was then treated with compound 11, in toluene, to afford 13 in 47% yield for two steps. The coupling of furans 23 or 25 to some derivative of 13 was then examined. With this in mind, compounds 17 and 20 were prepared (Schemes 4 and 5). Compound 13 (Scheme 4) was treated with sodium hydride and methoxymethyl chloride to give 14 in 66% yield. Deprotection of 14 with tetrabutylammonium fluoride produced alcohol 15 in quantitative yields. Iodide 17 was then prepared, in nearly quantitative yield (two steps), from alcohol 15, *via* mesylate 16 (Scheme 4).

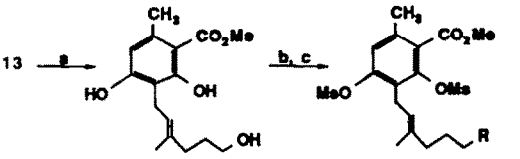
The route to compound 20 proceeded as follows. Alcohol 18 was prepared in 89% yield by treating 13 with tetrabutylammonium fluoride (Scheme 5). Compound 19 was obtained from the reaction of alcohol 18 with mesyl chloride and triethylamine. Compound 19 was converted to the corresponding iodide (20) in 97% yield using sodium iodide in acetone (Scheme 5). All attempts to couple 23 with either mesylate 19 or iodide 20 failed.

Scheme 3



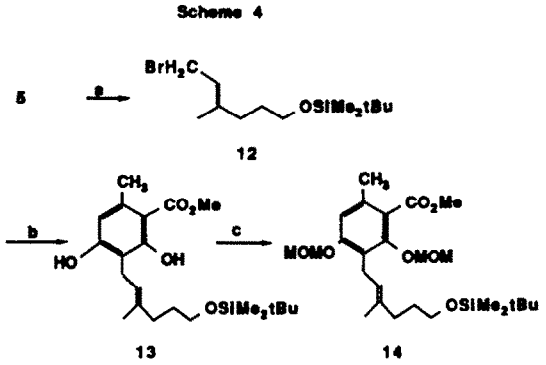
[a] NaH, n-BuLi, Δ ; [b] HCl; [c] KOH, EtOH, Et_2O.

Scheme 5



[a] n-$BuN_4N^+F^-$; [b] MsCl, Et_3N; [c] NaI, acetone.

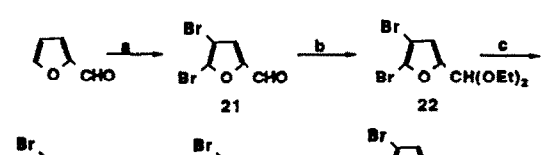
Scheme 4



[a] Ph_3P, CBr_4; [b] toluene, 11 , Δ ; [c] NaH, MOMCl; [d] n-$Bu_4N^+F^-$; [e] MsCl,Et_3N; [f] NaI, acetone

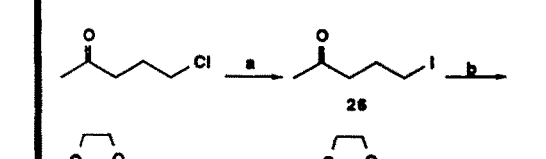
The 2,4-disubstituted furan moiety was prepared from furfural as shown in Scheme 6.[6] Furfural was treated with bromine and aluminum chloride to afford compound 21 in 47% yield. The aldehyde function was protected as its diethyl acetal in 84% yield. Selective metal-halogen exchange with n-butyllithium, followed by acid workup, gave compound 23 in 89% yield. Deprotection of 23 with 5% hydrochloric acid gave aldehyde 24 (83% yield). Compound 24 was subjected to a Wittig reaction to give an unstable substituted furan (25) in 78% yield. Because of the sensitive nature of 25, the more stable compound 23 was chosen for the coupling reactions. In a model study (Scheme 7), compound 28 was prepared in 44% yield by treatment of 23 with n-butyl- lithium (metal-halogen exchange), followed by addition of compound 27 (prepared in two steps, 78% yield). Deprotection of the diethyl acetal with deuterated chloroform gave aldehyde 28. The overall yield of 44%, required the addition of hexamethylphosphoramide (HMPA) in the coupling procedure. Without this additive, yields were considerably lower (~13%).

Scheme 6



[a] $AlCl_3$, Br_2; [b] NH_4NO_3, $HC(OEt)_3$; [c] 1. n-BuLi, 2. H^+; [d] 2N HCl; [e] Isopropyl triphenylphosphonium iodide.

Scheme 7

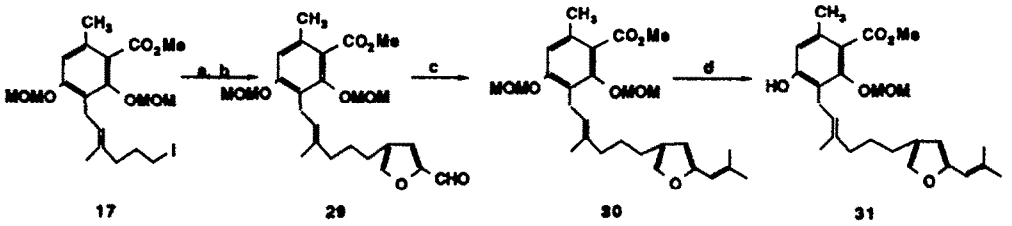


[a] NaI, acetone; [b] ethylene glycol, TsOH; [c] 23, n-BuLi; [d] $CDCl_3$

Compound 17 was coupled to furan 23 and the diethyl acetal then deprotected with deuterated chloroform to afford aldehyde 29 in two steps and an overall yield of 47% (Scheme 8). Aldehyde 29 was subjected to a Wittig reaction to give compound 30 in 75% yield. This key intermediate only requires deprotection of the phenolic groups and hydrolysis of the ester to give cristatic acid. Our past experience with similar molecules[3] has shown that this deprotection is not a trivial

operation. Although Hiyama and co-workers[7] have shown that the SEM group can be a useful protecting group for compounds of this nature, we have been unable to achieve satisfactory yields. Furthermore, the sensitive nature of 30, due to the presence of a very electron-rich furan ring, does not make the SEM group a very useful alternative. Our previous experience with colletochlorin D[8] has shown that methyl ethers are not suitable protecting groups because the 2-position cannot be deprotected. Therefore, we chose the methoxymethyl ethers for protecting the phenolic groups. All attempts to remove them either failed (resulting in extensive decomposition), or deprotected only one group to give compound 31. Trimethylsilyl iodide and triphenylmethyl carbonium fluoborate[9] produced decomposition of the molecule, while p-toluenesulfonic acid[10] and hydrochloric acid[11] afforded 31. Future investigations will focus on finding suitable protecting groups as well as preparing other derivatives of potential biological interest.

Scheme 8



[a] n-BuLi, 23; [b] $CDCl_3$; [c] n-BuLi, isopropyl triphenylphosphonium iodide; [d] MeOH, conc. HCl (cat.).

EXPERIMENTAL

^{1}H-NMR spectra were obtained in the designated solvents on a Bruker WM 250 (MHz), IBM/Bruker AF 250 (MHz), or Bruker AM 500 (MHz) Fourier transform spectrometers. Chemical shifts are in parts per million (δ) relative to tetramethysilane. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). High resolution mass spectra were obtained on a V.G. Micromass 7070-H high resolution mass spectrometer or a V.G. Zab-E mass spectrometer interfaced with a V.G. analytical data system. Infrared spectra (IR) were obtained on a Perkin-Elmer model 281 B spectrometer, as thin films on sodium chloride plates, or as potassium bromide disks (KBr pellets); absorptions are recorded in cm^{-1}. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at Desert Analytics Organic Microanalyses P.O. Box 41838, Tucson, AZ85717. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (250μm) with a fluorescent indicator supplied by E. Merck (silica gel 60). Visualization was effected with ultraviolet light (UV), 254nm, 7% W/V ethanolic 12-phosphomolydic acid (PMA), anisaldehyde solution (5% in ethanol, 5% sulfuric acid) or 0.4% W/V 2,4-dinitrophenylhydrazine in 2N HCl (DNP). Preparative thin layer chromatography (PTLC) was performed on precoated silica gel plates (1000μm) with a fluorescent indicator, supplied by Analtech, Inc. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). All solvents used were reagent grade. Anhydrous diethyl ether, tetrahydrofuran (THF), benzene and toluene were distilled from sodium and benzophenone; methanol was distilled form magnesium turnings and a small amount of iodine; methylene chloride was distilled from calcium hydride; N,N-dimethylformamide (DMF) was dried over magnesium sulfate and distilled under reduced pressure.

5-O-tert-Butyldimethylsilyl-2-pentanone 3. 3-Acetyl-1-propanol (2.00 g, 19.6 mmol) was placed in dry DMF (25ml) under argon. *tert*-Butyldimethylsilyl chloride (5.90 g, 39.2 mmol) and imidazole (5.33 g, 78.3 mmol) were added to the solution, which was then heated at 70°C for 24 h. The solution was then cooled, diluted with water (60ml) and washed (3 X 30 ml) with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The concentrated material was then chromatographed (5% Et_2O-pet. ether) to yield pure 3 in 85% yield (3.57 g). IR (neat) 2970, 2945 (CH) 1720 (C=O). ^{1}H-NMR ($CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.78 (m, 2H), 2.15 (s, 3H), 2.50 (t, 2H), 3.61 (t, 2H). R_f 0.53 (20% Et_2O-pet. ether).

Ethyl (E)-6-O-tert-Butyldimethylsilyl-3-methyl-2-hexenoate 4a. Triethyl phosphonoacetate (21.05 g, 93.88 mmol) was added dropwise to a stirred solution of NaH (2.52 g, 105.1 mmol hexane) in dry THF at 0°C under argon and allowed to stir for 10 min. Compound 3 (16.25 g, 75.1 mmol) in 50 ml of dry THF was then added to the solution via a syringe. The reaction was allowed to warm to room temperature and stirred for 40 h. The reaction was diluted with 250 ml of ether and washed with saturated NH_4Cl and saturated NaCl solutions. The ether layer was dried with Na_2SO_4 and concentrated *in vacuo*. Compound 4a was separated from its *cis* isomer 4b by flash column chromatography (5% Et_2O-pet. ether), to give compounds 4a (17.25g) and 4b (1.75g) in a 10 to 1 ratio. IR (neat) 2970, 2950 (CH), 1720 (C=O), 1650 (C=C). ^{1}H-NMR ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H),

1.27 (t, 3H), 1.69 (m, 2H), 2.16 (d, 3H), 2.20 (t, 2H), 3.60 (t, 2H), 4.15 (q, 2H), 5.67 (m, 1H). R_f 0.68 (20% Et_2O-pet. ether).

(E)-6-O-*tert*-Butyldimethylsilyl-3-methyl-2-hexene-1-ol 5. Compound 4a (18.50g, 57.6 mmol) and CH_2Cl_2 (500 ml) were cooled to -78°C, under argon. To this stirred solution was added a 1.0 M solution of DIBAL (144.0ml). The reaction was allowed to stir 1 h at -78°C, and then warmed to 0°C and diluted with a saturated solution of potassium sodium tartrate and 500 ml of ether. The layers were separated and the aqueous layer was extracted with 3 X 100 ml of ether. The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo*. The concentrate was purified by flash column chromatography (50% Et_2O-pet. ether), to yield 13.5g (96% yield) of compound 5, IR(neat) 3330 (OH), 2970, 2960 (CH). ^{1}H-NMR ($CDCl_3$) 0.04 (s, 6H), 0.89 (s, 9H), 1.37 (s, 1H), 1.61 (m, 2H), 1.65 (s, 3H), 2.06 (t, 2H), 3.60 (t, 2H), 4.14 (d, 2H), 5.42 (m, 1H). R_f 0.25 (Et_2O-pet. ether). Anal. Calcd. for $C_{13}H_{28}SiO_2$: C, 63.89; H, 11.55%. Found: C, 64.02; H, 11.86%.

Ethyl (E)-6-chloro-3-methyl-2-hexenoate 6a. Triethyl phosphonoacetate (4.65g, 20.73 mmol) was added at -78°C to a solution of LDA (20.73 mmol) and dry THF (40 ml) under argon. The mixture was warmed to 0°C for 15 min. then cooled to -78°C. Freshly distilled 5-chloro-2-pentanone (2.00g, 16.59 mmol) was added to the solution dropwise. The solution was slowly warmed to 0°C and held at this temperature for 36h. The reaction was then quenched with saturated NH_4Cl solution (20ml) and separated. The organic phase was washed with 20 ml saturated NH_4Cl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The product was then purified by flash column chromatography (10% EtOAc-hexane) to give compounds 6a (1.55g) and 6b (0.98) in a 1.6 to 1 ratio, (80% yield). IR (neat) 3010, 3000 (CH), 1730 (C=O), 1670 (C=C). ^{1}H-NMR ($CDCl_3$) 1.28 (t, 3H), 1.95 (m, 2H), 2.16 (d, J=0.8, 3H), 2.30 (t, 2H), 3.53 (t, 2H), 4.15 (q, 2H) 5.69 (d, J=0.8, 1H). R_f 0.50 (25% EtOAc-hexane).

(E)-6-Chloro-3-methyl-2-hexene-1-ol 7. A 1.0 M solution of DIBAL (18.8 ml) was added dropwise at -78°C under argon to a stirred solution of compound 6a (1.63g, 8.5 mmol) and dry CH_2Cl_2 (60 ml). The reaction was allowed to stir for 1 h at -78°C, warmed to 0°C and quenched with saturated potassium sodium tartrate (100 ml). After diluting with 200 ml of ether, the organic phase was separated. The aqueous phase was washed with ether (2 X 100 ml) and the organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The product was chromatographed (25% EtOAc-hexane) to give 1.21 g (95% yield) of compound 7. IR (neat) 3350, (OH), 2970, 2960, (CH), 1660 (C=C). ^{1}H-NMR ($CDCl_3$) 1.32 (d, J=1, 1H, D_2O exchange), 1.68 (s, 3H), 1.90 (m, 2H), 2.17 (t, 2H), 3.52 (t, 2H), 4.16 (dd, J=1.0, 7.0, 2H), 5.45 (dt, J=7.0, 1H). R_f 0.22 (25% EtOAc-hexane).

(E)-1-O-*tert*-Butyldimethylsilyl-6-chloro-3-methyl-2-hexene 8. *tert*-Butyldimethylsilyl chloride (1.47g, 9.7 mmol) and imidazole (1.33g, 19.5 mmol) were added at 0°C to a stirred solution of compound 7 (1.21g, 8.10 mmol) and 20 ml of dry DMF. The mixture was stirred for 1.5 h, diluted with 75ml H_2O and 100 ml of ether. The organic layer was separated, washed with saturated NaCl solution (20ml), dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by flash column chromatography (5% EtOAc-hexane) to give 2.01g, (95% yield) of compound 8. IR (neat) 2980, 2950, 2880 (CH), 1670 (C=C). ^{1}H-NMR ($CDCl_3$) 0.07 (s, 6H), 0.90 (s, 9H), 1.63 (s, 3H) 1.87 (m, 2H), 2.14 (t, 2H), 3.52 (t, 2H), 4.19 (d, J=6.3, 2H) 5.34 (t, J=6.3 1H). R_f 0.82 (25% EtOAc-hexane). HRMS, M-H/e, Calcd. for $C_{13}H_{27}SiCl0$, 261.44. Found, 261.146

(E)-1-O-*tert*-Butyldimethylsilyl-6-iodo-3-methyl-2-hexene 9. A mixture of compound 8 (0.20g, 0.76 mmol) and NaI (1.13g, 7.6 mmol) were heated to reflux in 5 ml of acetone under argon for 20 h. The solution was cooled, diluted with ether (100 ml) and washed with 50 ml of saturated NaCl solution and 20 ml of 20% $Na_2S_2O_3$ solution. The solvent was removed *in vacuo* to give 0.260g (96% yield) of compound 9. IR (neat) 2970, 2950 (CH), 1660 (C=C). ^{1}H-NMR ($CDCl_3$) 0.07 (s, 6H), 0.90 (s, 9H), 1.62 (s, 3H), 1.93 (m, 2H), 2.10 (t, 2H), 3.16 (t, 2H), 4.18 (d, J=6.3, 2H) 5.35 (t, J=6.3, 1H). R_f 0.81 (25% EtOAc-hexane). HRMS, M-H/e, Calcd. for $C_{13}H_{27}SiIO$, 353.080. Found, 353.075.

Methyl orsellinate 10.[5,12] Methyl acetoacetate (20.0g, 172.2 mmol) was added dropwise to a stirred solution of NaH (6.2g, 258.4 mmol; washed with hexane), and 100 ml of dry THF at 0°C under argon. The solution was then cooled to -78°C and a 2.6 M solution of n-BuLi (63 ml, 163.6 mmol) was added. The solution was warmed to room temperature and stirred overnight. It was then refluxed for 24 h. The solution was cooled, acidified to pH 1.5-2.0 and stirred overnight. The mixture was then extracted with ethyl acetate (2 X 100ml), dried over Na_2SO_4 and concentrated *in vacuo*. The concentrate was purified by flash column chromatography (25% EtOAc-hexane) to give a 61% yield (9.50 g) of compound 10. IR (KBr pellet). 3370 (OH), 2970 (CH), 1620 (C=O) ^{1}H-NMR ($CDCl_3$) 2.49 (s, 3H), 3.92 (s, 3H), 5.12 (br s, 1H), 6.23 (s, 1H), 6.28 (s, 1H), 11.77 (s, 1H). R_f 0.63 (50% EtOAc-hexane). m.p. 136-138°C.

Potassium methyl orsellinate 11. A 1.0M solution of KOH in ethanol (32.8 ml) was added at room temperature to a solution of compound 10 (6.0g, 32.6 mmol) in 50 ml of ether. The salt precipitated immediately. The solution was cooled in ice, and the salt collected and washed with pentane. It was dried overnight in a drying pistol (KOH, refluxing EtOAc) to afford 5.6g (78% yield) of compound 11.

(E)-1-Bromo-6-O-*tert*-butyldimethylsilyl-3-methyl-2-hexene 12. Carbon tetrabromide (6.8g, 20.4 mmol) and Ph_3P (5.2g, 19.6 mmol) were added in quick succession to a stirred solution of compound 5 (4.0g, 16.4 mmol) and dry CH_2Cl_2 (80 ml) at -78°C under argon. The reaction was allowed to stir for 1h, diluted with ether (100 ml), and then quickly passed through a column of silica gel. The solvent was removed *in vacuo* and the product was used immediately, without further purification, in the next step.

Methyl (E)-2,4-dihydroxy-6-methyl-3-[(6-O-*tert*-butyldimethylsilyl-3-methyl)-2-hexenyl]-benzoate 13.

Compound 11 (5.86 g, 26.6 mmol) and compound 12 (5.0g, 16.4 mmol theoretical) were placed in 80 ml of dry toluene under argon and refluxed for 12 h. The solution was cooled, and diluted with 100 ml of ether, washed with 1 X 20 ml saturated NH_4Cl solution, 1 X 20 ml saturated NaCl solution, and dried over Na_2SO_4. The product was concentrated *in vacuo* and purified by column chromatography (15% EtOAc-hexane) to yield 3.10 g (47% yield for two steps) of compound 13. An additional 2.0g of compound 10 were also recovered. IR (neat) 3400 (OH), 2970, 2940, (CH), 1650 (C=O), 1610 (C=C). ^1H NMR ($CDCl_3$) 0.04 (s, 6H), 0.90 (s, 9H), 1.62 (m, 2H), 1.81 (s, 3H), 2.98 (t, 2H), 2.48 (s, 3H), 3.43 (d, 2H), 3.59 (t, 3H), 3.91 (s, 3H), 5.28 (t, 1H), 6.21 (s, 1H), 12.05 (s, 1H). R_f 0.38 (20% Et_2O–pet. ether). HRMS, M-*tert*-Bu/e, Calcd. for $C_{18}H_{27}O_5Si$, 351.163. Found, 351.164.

Methyl (E)-2,4-di(methoxymethoxy)-6-methyl-3-[(6-O-*tert*-butyldimethylsilyl-3-methyl)-2-hexanyl]-benzoate 14. At 0°C, compound 13 was added to a solution of NaH (0.06g, 2.7 mmol; washed with hexane) and 10 ml of dry CH_2Cl_2 under argon. After 10 min, chloromethyl methyl ether (0.22g, 2.7m.moles) was added, the reaction was warmed to room temperature and stirred for 1h. The solution was washed with a saturated NH_4Cl solution (1 X 5ml), a saturated NaCl solution (1 X 5ml), dried with Na_2SO_4 and concentrated *in vacuo*. The product was purified by column chromatography (25% Et_2O–pet. ether) to yield 0.40g, of compound 14 (66% yield). IR (neat) 2970, 2940 (CH), 1730 (C=O) 1600 (C=C). ^1H-NMR ($CDCl_3$) 0.04 (s, 6H) 0.88 (s, 9H), 1.60 (m, 2H), 1.76 (s, 3H), 1.98 (t, 3H), 2.29 (s, 3H), 3.36 (d, 2H), 3.45 (s, 3H), 3.52 (s, 3H), 3.88 (s, 3H), 4.95 (s, 2H), 5.17 (s, 2H), 6.75 (s, 1H). R_f 0.26 (25% Et_2O–pet. ether). HRMS, M-H-OCH_3/e, Calcd. for $C_{25}H_{40}O_6Si$, 464.259. Found, 464.256.

Methyl (E)-3,4-di(methoxymethoxy)-6-methyl-3-[(3-methyl-6-ol)-2-hexenyl]-benzoate 15. A 1.0M solution of tetrabutylammonium fluoride (4 ml) was added to a stirred solution of 14 (0.40g, 0.8 mmol) and 5 ml of dry THF under argon. After 2h the reaction was diluted with ether (50 ml) and washed with water (2 X 20ml). The combined water extracts were extracted with ether (50 ml); the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by column chromatography (100% Et_2O) to give 0.30 grams (100% yield) of compound 15. IR (neat) 3450 (OH), 2950 (CH), 1720 (C=O), 1600 (C=C). ^1H-NMR ($CDCl_3$) 1.66 (m, 2H), 1.78 (s, 3H), 2.04 (t, 2H), 2.29 (s, 3H), 3.37 (d, 2H), 3.45 (s, 3H), 3.51 (s, 3H), 3.59 (t, 2H), 3.88 (s, 3H), 4.92 (s, 2H), 5.18 (s, 2H), 6.72 (s, 1H). R_f 0.34 (100% Et_2O), HRMS, M-H/e, Calcd. for $C_{20}H_{29}O_7$, 381.191. Found, 381.193.

Methyl (E)-2,4-di(methoxymethoxy)-6-methyl-3-[[3-methyl-6-(methylsulfonyl)]-2-hexenyl]-benzoate 16. At 0°C, under argon, triethylamine (0.17g, 1.7 mmol) and mesyl chloride (0.18g, 1.6 mmol) were added in sequence to a stirred solution of compound 15 (0.30g, 0.78mmol) and 10 ml of dry CH_2Cl_2. After 0.5h the reaction mixture was diluted with ether (50 ml), washed with saturated $NaHCO_3$ solution (10 ml), dried over Na_2SO_4 and concentrated *in vacuo*. Purfication by column chromatography (100% Et_2O) yielded 0.36g, (100% yield) of compound 16. IR (neat) 2950 (CH), 1720 (C=O), 1600 (C=C). ^1H-NMR ($CDCl_3$) 1.77 (s, 3H), 1.82 (m, 2H), 2.07 (t, 2H), 2.19 (s, 3H), 2.90 (s, 3H), 3.36 (d, 2H), 3.45 (s, 3H), 3.52 (s, 3H), 3.89 (s, 3H), 4.12 (t, 2H), 4.95 (s, 2H), 5.21 (s, 2H), 6.72 (s, 1H). R_f 0.50 (100% Et_2O). HRMS, M/e, Calcd. for $C_{21}H_{32}O_9S$, 460.177. Found 460.173.

Methyl (E)-2,4-di(methoxymethoxy)-6-methyl-3-[(6-iodo-3-methyl)-2-hexenyl]-benzoate 17. To a stirred solution of compound 16 (0.36g, 0.78 mmol) and acetone (20 ml) was added 1.16g NaI (7.8 mmol). The solution was then heated at 50°C for 4h. After cooling, the solution was diluted with ether (100 ml), washed with a 50:50 v/v solution of saturated $NaHCO_3$ and 20% $Na_2S_2O_3$ solution (20 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The product was then purified by column chromatography (40% Et_2O–pet. ether) to yield 0.34g (94% yield) of compound 17. IR (neat) 2950 (CH), 1720 (C=O), 1585 (C=C). ^1H-NMR ($CDCl_3$) 1.76 (s, 3H), 1.91 (m, 2H), 2.04 (t, 2H), 2.31 (s, 3H), 3.13 (t, 2H), 3.36 (d, 2H), 3.48 (s, 3H), 3.54 (s, 3H), 3.91 (s, 3H), 4.95 (s, 2H), 5.18 (s, 2H), 6.74 (s, 1H). R_f 0.43 (40% Et_2O–pet. ether). HRMS, M-H/e, Calcd. for $C_{20}H_{28}O_6I$, 491.093. Found 491.087.

Methyl (E)-2,4-dihydroxy-6-methyl-3-[(3-methyl-6-ol)-2-hexenyl]-benzoate 18. A 1.0 M solution of tetrabutylammonium fluoride (4.9 ml) was added to a stirred solution of compound 13 (0.50g, 1.22 mmol) and 20 ml of dry THF. The reaction was stirred for 4h under argon, diluted with ether (100 ml) washed with water (3 X 15 ml), saturated NaCl solution (1 X 20 ml), dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography (80% Et_2O–pet. ether) afforded pure 18, 0.32g, (89% yield). IR (neat) 3140 (OH), 2990, 2970, (CH) 1745 (C=O), 1580 (C=C). ^1H-NMR ($CDCl_3$) 1.72 (m, 2H), 1.83 (s, 3H), 2.14 (t, 2H), 2.44 (s, 3H), 3.41 (d, 2H), 3.67 (t, 2H), 3.92 (s, 3H), 5.31 (t, 1H), 6.17 (s, 1H), 12.05 (s, 1H). R_f 0.80. (100% ether). HRMS, m/e, Calcd. for $C_{16}H_{22}O_5$, 294.147. Found 294.148.

Methyl (E)-2,4-di(methylsulfonyl)-6-methyl-3-[(3-methyl-6-methylsulfonyl)-2-hexenyl]-benzoate 19. At 0°C, under argon, triethylamine (28mg, 0.28 mmol) and mesyl chloride (29mg, 0.25 mmol) were added to compound 18 (15mg, 0.05 mmol) and 5ml of dry CH_2Cl_2. The reaction was stirred for 0.5 h, diluted with ether (50ml), washed with saturated $NaHCO_3$ solution (10ml), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (100% Et_2O) to yield 26.2mg (100% yield) of compound 19. IR (neat) 2970, 2950 (CH), 1730 (C=O), 1610 (C=C). ^1H-NMR ($CDCl_3$) 1.78 (s, 3H), 1.87 (m, 2H), 2.10 (t, 2H), 2.39 (s, 3H), 2.95 (s, 3H), 3.21 (s, 3H), 3.26 (s, 3H), 3.54 (d, 2H), 3.95 (s, 3H), 4.18 (t, 2H), 5.18 (t, 1H), 7.27 (s, 1H). R_f 0.21 (100% Et_2O). HRMS, M^+NH_4/e, Calcd. for $C_{19}H_{32}O_{11}S_3N$, 546.110. Found 546.115.

Methyl (E)-2,4 di(methylsulfonyl)-6-methyl-3-[(6-iodo-3-methyl)-2-hexenyl]-benzoate. 20. Compound 19 (25.0mg 0.047 mmol) was added to a stirred solution of NaI (71mg 0.47 mmol) and acetone (10ml) under argon. The reaction was heated at 50°C for 16h, cooled, diluted with ether, washed with 50:50 v/v mixture of saturated $NaHCO_3$ solution and 20% $Na_2S_2O_3$ solution, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (100% ether) yielded 25.4mg (97%

yield) of compound **20**. IR (neat) 3020, 2960 (CH), 1730 (C=O), 1610 (C=C). ^{1}H NMR ($CDCl_3$) 1.76 (s, 3H), 1.92 (m, 2H), 2.08 (t, 2H), 2.37 (s, 3H), 3.13 (t, 2H), 3.18 (s, 3H), 3.26 (s, 3H), 3.55 (d, 2H), 3.82 (s, 3H), 5.18 (t, 1H), 7.27 (s, 1H). R_f 0.55 (100% ether). HRMS, M/e, Calcd. for $C_{18}H_{25}S_2O_5I$, 560.004. Found 560.001.

4,5-Dibromo-2-furancarboxyaldehyde 21.[6,12] Freshly distilled furfural (20.0g, 208 mmol) was added dropwise at 0°C, under argon, to aluminum chloride (61.0g, 456mmol) from an addition funnel, over a period of 2h, with mechanical stirring. Bromine (67.0g, 416m.moles) was then added in a similar manner over a 2h period. Stirring was then discontinued and the reaction was allowed to stand overnight. The mixture was poured into ice (200g), diluted with 200ml of ether and the layers separated. The aqueous layer was then extracted with 2 X 50ml of ether and the organic extracts were combined and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the remaining mixture was distilled (82-86°C, 5mm) to give 24.88g (47% yield) of compound 21. IR ($CHCl_3$) 1690 (C=O). ^{1}H NMR ($CDCl_3$) 7.24 (s, 1H) 9.53 (s, 1H). R_f 0.30 (10% EtOAc-hexane). m.p. 36-37°C.

4,5-Dibromo-2-(diethoxymethyl)-furan 22.[6,12] Triethyl orthoformate (11.6g, 78.7mmol) and ammonium nitrate (0.25g, 5mole%) were added to a stirred solution of compound 21 (5.00g, 19.7 mmoles) and absolute ethanol (100ml), under argon, and refluxed for 4h. The solution was concentrated *in vacuo*, diluted with 50ml of ether and washed with 1 X 10ml of saturated NaCl solution. The solution was dried over Na_2SO_4, concentrated and chromatographed (5% EtOAc-hexane) to yield 5.45g (84% yield) of compound 22. IR ($CDCl_3$) 2990, 2960, 2930 (CH). ^{1}H-NMR ($CDCl_3$) 1.24 (t, 3H), 3.60 (q, 2H), 5.45 (d, J=0.6, 1H), 6.50 (d, J=0.6, 1H). R_f 0.48 (10% EtOAc-hexane).

4-Bromo-2-(diethoxymethyl)-furan 23.[6,12] A 1.6M solution of n-BuLi (8.4ml, 12.96 mmol) was added to a stirred solution of compound 22 (4.25g, 12.90 mmol) and dry ether (50ml) at -78°C, under argon. The solution was allowed to warm to 0°C over a 2h period. It was then quenched with water (10ml) and acidified to pH 5.0 with 5% HCl. The ether layer was separated, dried over Na_2SO_4 and chromatographed (3% EtOAc-hexane) to yield 2.87g (89% yield) of compound 23. IR (neat) 2990, 2940, 2890 (CH). ^{1}H-NMR ($CDCl_3$) 1.24 (t, 3H), 3.62 (q, 2H), 5.50 (s, 1H), 6.48 (s, 1H), 7.41 (s, 1H). R_f 0.45 (10% EtOAc-hexane).

4-Bromo-2-furancarboxyaldehyde 24.[6,12] Compound 23 (7.85g, 31.5 mmol) was added to 40ml of a 2N HCl solution at room temperature and allowed to stir for 15 minutes. The solution was diluted with ether (50ml) and separated. The ether layer was washed with saturated solutions of $NaHCO_3$ (10 ml) and NaCl (10 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The concentrate was purified by flash column chromatography (10% EtOAc-hexane) to yield 4.45g (83% yield) of compound 24. IR ($CHCl_3$) 1685 (C=O). ^{1}H-NMR ($CDCl_3$) 7.26 (d, J=0.4, 1H), 7.68 (s, 1H), 9.63 (d, J=0.4, 1H), R_f 0.24 (10% EtOAc-hexane). m.p. 54.5-56.0°C.

4-Bromo-2-[(2-methyl)-1-propenyl]furan 25. In a flame-dried flask, under argon, at -78°C, 1.6 M solution of n-BuLi (4.1ml, 6.58mmol) was added to a stirred solution of isopropyl triphenylphosphonium iodide (2.97g, 6.86mmol) and dry THF (45ml). The heterogeneous solution was warmed to 0°C for 20 min to give a red homogeneous solution which was then cooled to -78°C. Compound 24 (0.96g, 5.5mmol) in 10ml of dry THF was then added dropwise to the solution and stirred for 30 min. The reaction was warmed to room temperature, stirred 30 minutes and quenched with saturated NH_4Cl solution (20ml). After dilution with ether (100ml), the organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The material was then purified by column chromatography (1% EtOAc-hexane) to yield 0.86g (78% yield) of compound 25. IR (neat) 2990, 2940, 2780 (CH), 1660 (C=C). ^{1}H-NMR ($CDCl_3$) 1.90 (s, 3H), 1.95 (s, 3H), 5.99 (d, 1H), 6.20 (s, 1H), 7.31 (s, 1H). R_f 0.63 (5% EtOAc-hexane). HRMS, m/e, Calcd. for C_8H_9BrO, 199.983. Found 199.985.

5-Iodo-2-pentanone 26. Sodium iodide (31.1g, 207.5mmol) was added to a stirred solution of freshly distilled 5-chloro-2-pentanone (5.00g, 41.5mmol) and 250ml of acetone, under argon. The reaction was refluxed overnight, cooled, diluted with ether (250ml), washed with a 50:50 v/v solution of saturated $NaHCO_3$ and 20% $Na_2S_2O_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by column chromatography to yield 7.50g (85% yield) of compound 26. IR (neat) 2970 (CH), 1710 (C=O). ^{1}H-NMR ($CDCl_3$) 2.06 (m, 2H), 2.18 (s, 3H), 2.62 (t, 2H), 3.03 (t, 2H). R_f 0.24 (25% Et_2O-pet. ether).

2-Methyl-2-(3-iodo)propyl-1,3-dioxolane 27. Compound 26 (7.50g, 35.4mmol) was added to a stirred solution of reagent grade benzene (250ml), ethylene glycol (6.60g, 106.2mmol) and toluene sulfonic acid (0.08g, 1 mole %), fitted with a Dean Stark trap and refluxed for 3h. The reaction mixture was cooled, washed with saturated solutions of $NaHCO_3$ (20ml), and NaCl (20ml), dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by column chromatography to give 8.32 (92%yield) of compound 27. IR (neat) 2980, 2960, 2890 (CH). ^{1}H-NMR ($CDCl_3$) 1.32 (s, 3H), 1.76 (m, 2H), 1.95 (m, 2H), 3.21 (t, 2H), 3.92 (m, 4H). R_f 0.32 (25% Et_2O-pet. ether).

2-[3-(3-Furanyl-5-carboxyaldehyde)]propyl-2-methyl-1,3-dioxolane 28. A 1.5M. solution of n-BuLi (1.41ml, 2.12mmol) was added dropwise at -78°C, under argon, to compound 23 (0.53g, 2.12mmol), HMPA (0.36, 2.12mmol) and dry THF (20ml). After stirring for 1h, compound 27 (2.73g, 10.64mmol) in 2ml of dry THF was added dropwise to the mixture. The solution was allowed to slowly warm to room temperature and stir overnight. The reaction mixture was diluted with ether (50ml), washed with saturated solutions of NH_4Cl and NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was diluted with 5ml of $CDCl_3$ and allowed to stand overnight at 0°C. After concentrating the solution, the product was purified by column chromatography to yield 0.2g (44% yield) of compound 28. IR (neat) 2990, 2950, 2890 (CH), 1680 (C=O). ^{1}H-NMR ($CDCl_3$) 1.34 (s, 3H), 1.69 (m, 4H), 2.49, (t, 3H), 3.92 (m, 4H), 7.12 (s, 1H), 7.47 (s, 1H), 9.58 (s, 1H). R_f 0.26 (50% Et_2O-pet. ether) HRMS, M^+H/e, Calcd. for $C_{12}H_{17}O_4$, 225.113. Found 225.112.

Methyl (E)-2,4-di(methoxymethoxy)-6-methyl-3-[3-methyl-6-(furanyl-5-carboxyaldehyde]-2-hexenyl] -benzoate 29. A 1.6 M solution of n-BuLi (1.5 ml, 2.4 mmol) was added to a stirred solution of compound **23** (0.60g, 2.4 mmol) and 8 ml of dry THF at -78°C, under argon. After 15 min 0.5 ml of dry HMPA was added, after 15 additional min, compound 17 (0.34g, 0.69 mmol) in 2 ml of dry THF (at -78°C) was added to the solution dropwise. The reaction was allowed to slowly warm to room temperature and to stir overnight. The reaction was then diluted with ether (50 ml), washed with saturated NH_4Cl, (1 X 10 ml), saturated NaCl (1 X 10 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was then diluted with 2 ml of $CDCl_3$ and allowed to stand overnight at 0°C. Concentration of the solution, and purification of the product by column chromatography (40% Et_2O-pet. ether) afforded 0.15g, (47% yield) of compound **29**. IR (neat) 2970, 2950, (CH), 1720 (C=O), 1680 (C=O), 1600 (C=C). ^1H NMR ($CDCl_3$) 1.65 (m, 2H), 1.72 (s, 3H), 1.98 (t, 2H), 2.28 (s, 3H), 2.39 (t, 2H), 3.36 (d, 2H), 3.44 (s, 3H), 3.52 (s, 3H), 3.86 (s, 3H), 4.94 (s, 2H), 5.17 (s, 2H), 6.74 (s, 1H), 7.07 (s, 1H), 7.42 (s, 1H), 9.59 (s, 1H). R_f 0.20 (40% Et_2O-pet. ether). HRMS, M/e, Calcd. for $C_{25}H_{32}O_8$, 460.210. Found 460.212. Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01%. Found: C, 65.60; H, 6.91%.

Methyl (E)-2,4 di(methoxymethoxy)-6-methyl-3-[3-methyl-6-[5-(2-methyl-1-propenyl)-3-furanyl] -2-hexenyl]-benzoate 30. A 1.6M solution of n-BuLi (0.3 ml, 0.49 mmol) was added at -78°C, under argon, to a stirred solution of isopropyl triphenylphosphonium iodide (0.21g, 0.44 mmol) and 5 ml of dry THF. The reaction was then warmed to 0°C for 20 min to give a red homogeneous solution, which was then cooled to -78°C again. Compound **29** (0.15g, 0.32 mmol) in 5 ml of dry THF was then added dropwise to the reaction mixture. The reaction was stirred at -78°C for 30 min warmed to 0°C, and stirred an additional 30 min. The reaction was diluted with 50 ml of ether, washed with saturated NH_4Cl, solution, saturated NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by column chromatography (25% Et_2O-pet. ether) to give 0.12 grams (75% yield) of compound **30**. IR (neat) 2930 (CH), 1730 (C=O), 1600 (C=C). ^1H-NMR (C_6D_6) 1.61 (m, 2H), 1.68 (s, 3H), 1.79 (s, 3H), 1.90 (s, 3H), 2.01 (t, 2H), 2.22 (s, 3H), 2.17 (t, 2H), 3.16 (s, 3H), 3.38 (s, 3H), 3.54 (s, 3H), 3.67 (d, 2H), 4.86 (s, 2H), 5.08 (s, 2H), 5.49 (m, 1H), 6.05 (s, 1H), 6.16 (s, 1H), 6.75 (s, 1H), 6.98 (s, 1H). R_f 0.44 (40% Et_2O-pet. ether). HRMS, M/e, Calcd. for $C_{28}H_{38}O_7$, 486.261. Found 486.257.

Methyl (E)-4-hydroxy-2-methoxymethoxy-6-methyl-3[3-methyl-6-[5-(2-methyl-1-propenyl)-3-furanyl] -2-hexenyl]-benzoate 31. Compound **30** (10.0mg, 0.02 mmol) was added to 5 ml of methanol containing a trace of concentrated HCl, and the mixture stirred overnight. The reaction was diluted with ether (50 ml), washed sequentially with saturated solutions of NH_4Cl and NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (25% Et_2O-pet. ether) to give 6.5 mg (74% yield) of compound **31**. IR ($CHCl_3$) 3400 (OH) 3010, 2990, 2850, (CH), 1730 (C=O) 1650, 1610, (C=C). ^1H-NMR (C_6D_6) 1.60 (s, 3H) 1.62 (m, 2H), 1.67 (s, 3H), 1.78 (s, 3H), 2.05 (m, 2H), 2.16 (m, 2H), 2.26 (s, 3H), 3.14 (s, 3H), 3.18 (s, 3H), 3.70 (m, 2H), 4.86 (s, 2H), 5.68 (m, 1H), 5.89 (s, 1H), 5.99 (S, 1H), 6.11 (s, 1H), 6.55 (s, 1H), 7.46 (s, 1H). R_f 0.61 (33% Et_2O pet. ether). HRMS, M/e, Calcd. for $C_{26}H_{34}O_6$, 442.236. Found 442.234.

Acknowledgment. We thank Merck, Sharp and Dohme Laboratories and the National Science Foundation for partial support of these investigations.

REFERENCES

1. Zechlin, L., Wolf, M., Steglich, W., Anke, T., *Liebigs Ann. Chem.* **1981**, 2099.

2. Steglich, W., *Pure & Appl. Chem.* **1981**, 53, 1233.

3. Chen, K-M., Semple, J.E., Joullié, M.M., *J. Org. Chem.* **1985**, 50, 3997.

4. Safaryn, J.E., Chiarello, J., Chen, K-M., Joullié, M.M., *Tetrahedron* **1986**, 42, 2635.

5. Barrett, A.G.M., Morris, T.M., Barton, D.H.R., *J. Chem. Soc., Perkin I* **1980**, 2272.

6. Chadwick, D.J., Chambers, J., Hodgson, P.K.G. Meakins, G.D., Snowden, R.L., *J. Chem. Soc., Perkin I* **1974**, 1141.

7. Saimoto, H., Kusano, Y., Hiyama, T., *Tetrahedron Lett.* **1986**, 27, 1607.

8. Guthrie, A.E., Semple, J.E., Joullié, M.M., *J. Org. Chem.* **1982**, 47, 2369.

9. Nakata, T., Uranesic, B., Okigawa, M., Smith-Palmer, T., Kishi, Y., *J. Amer. Chem. Soc.* **1978**, 100, 2933.

10. Monti, H., Leandri, G., Klos-Ringoet, M., Corriol, C., *Synth. Comm.* **1983**, 13, 1021.

11. Auerbach, J., Weinreb, S.M., *J. Chem. Soc., Chem. Comm.* **1974**, 298.

12. All physical data are in agreement with the literature values.